Remarks/Arguments

Claims 1 and 3-6 are currently pending in the instant application. The Examiner has rejected claims 1 and 4-6 under 35 U.S.C. §103(a) as obvious over *Hcaplus Abstract* 2001:167983 (WO 200101621, *Cosford et. al.*) in further view of *Blake et al.* and in further view of *Patani et. al.* Applicant respectfully traverses this rejection.

The Examiner alleges that *Hcaplus Abstract* 2001:167983 teaches the compound

which differs from the instantly claimed compound in the following two structural aspects:

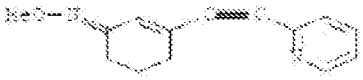
1) the 2 position of the pyridyl ring in the prior art compound is unsubstituted, i.e. it is a hydrogen, whereas the 2 position of the pyridyl ring in the instantly claimed invention is a non-radiolabeled methyl; and
2) the substituent on the cyclohexene ring of the prior art compound has a non-radiolabeled O-methyl oxime substituent whereas the instantly claimed invention has a radiolabeled O-C_{1-4} alkyl oxime substituent.

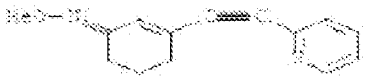
The Examiner next alleges that *Patani* discloses the concept of bioisosterism, namely "compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties" and that "bioisosteres affect the same pharmacological target as agonists or antagonists, thereby having biological properties that are related. The Examiner further alleges that *Patani* teaches that "methyl is a bioisosteric replacement for hydrogen."

The Examiner next alleges that *Blake* teaches that "stable isotopes are proving useful as tracers for drug distribution and metabolism studies." Lastly, the Examiner notes that *Cosford* teaches that  can "modulate metabotropic glutamate receptors."

Thus, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to synthesize radiolabeled bioisosteres of the compound of the *Hcaplus Abstract* for use as neuroimagers because radiolabeled compounds are useful as tracers for drug distribution and metabolism studies.

Applicant respectfully submits that the Examiner has not met the Patent Office's burden of establishing a *prima facie* case of obviousness under M.P.E.P §2143. The Examiner engages in a two part reconstruction of the instantly claimed invention from the prior art. The Examiner first suggests that it would have been obvious to modify the compound of the *Hcaplus*

Abstract,  , by adding a methyl group to the 2 position of the pyridyl ring; yet she provides no motivation to make this addition nor does she provide any motivation to make the addition at this specific position. Secondly, the Examiner suggests that it would be obvious to then radiolabel the resulting compound (i.e. the modified *Hcaplus Abstract* compound now with the methylated pyridyl ring); yet she provides no motivation to radiolabel this previously unknown compound.

Assuming, *arguendo*, that there was motivation to radiolabel a compound with ^{11}C or ^{3}H, which Applicant disputes, that motivation would have been to radiolabel the original *Hcaplus Abstract* compound, not the previously unknown compound which the Examiner has imagined for the purposes of this rejection. Why, given a perfectly good unsubstituted prior art compound, would one of ordinary skill in the art bother to first substitute that molecule before radiolabeling it?[1] The Examiner cannot presuppose the existence of the methylated compound for the purposes of demonstrating why there would be motivation to radiolabel that compound to arrive at the instantly claimed invention. Nor may she presuppose the existence of a radiolabeled *Hcaplus Abstract* molecule for the purposes of demonstrating why there would be motivation to add a methyl group at the 2 position on the pyridyl ring to arrive at the instantly claimed invention. Rather, she must demonstrated why one of ordinary skill in the art at the time the invention was made would have been motivated to modify the prior art compound, i.e.  , to <u>both</u> add a methyl group to the 2 position on the pyridyl ring <u>and</u> radiolabel said compound on the O-methyl oxime substituent. Even if the Examiner is able to provide motivation to add a methyl group or radiolabel said compound she has not demonstrated motivation to do <u>both</u> without presupposing the existence of either the radiolabeled compound or the methylated compound. Such presupposition is impermissible hindsight. Accordingly, a *prima facie* case of obviousness has not been established.

Even if it were permissible to engage in this two part hindsight reconstruction of the invention, the Examiner still cannot establish a *prima facie* case of obviousness. The Examiner asserts *Patani's* teachings of bioisosterism would motivate one of ordinary skill in the art to methylate the pyridyl ring of the *Hcaplus Abstract* compound. Applicant further reiterates the arguments made in the prior response. Despite all of the definitions of bioisosterism in *Patani* (i.e. the Langmuir Definition, Grimm's Hydride Displacement Law, and the Erlenmeyer Definition), none of which Applicant's claimed compound meets, the Examiner points to page

[1] Especially when, at least according to the Examiner's argument related to "bioisosterism", substituting the prior art compound would result in a compound with merely the <u>same</u> properties. Surely an artisan would not undertake a bothersome substitution for curiosity's sake.

3148 as stating that "[t]he critical component for bioisosterism is that bioisosteres affect the same pharmacological target as agonists or antagonists and, thereby, have biological properties which are related to each other." While it may be a necessary element of bioisosterism that bioisosteres have related biological properties, as stated in the article, this is a "component" of the theory. Accordingly, to be bioisosteres, compounds would still have to meet the other definitions disclosed in the paper, which the instantly claimed invention compared with the prior art compound disclosed in the *Hcaplus Abstract* does not.[2]

The Examiner asserts that "if fluorine, hydroxyl, NH2 and methyl are bioisosteres of one another and fluorine and hydrogen are bioisosteres of one another, one of ordinary skill in the art would be led to conclude that methyl and hydrogen are bioisosteres of one another." (p. 5 of the Official Action). Accepting this logic, *arguendo*, one of ordinary skill in the art would necessarily have to also conclude that hydrogen is a bioisosterer of hydroxyl, and NH_2. Following this logic one step further, one of ordinary skill in the art would also have to assume that hydrogen is also a bioisosterer of anything else that *Patani* discloses is a bioisosterer of fluorine, hydroxyl, NH_2 and methyl; such as thiol (p. 3151, Tables 7 and 8), CF_3 (p. 3152, Table 10), Cl (p. 3153), CN (p. 3154, Table 14), OCH_3 (p.3154, Table 14), and Br (p.3155, Table 16). Thus, instead of the isolated "teaching" of *Patani* that one could substitute hydrogen with methyl, one of ordinary skill in the art is left with the "teaching" that it is advantageous to substitute hydrogen with a plethora of possible substituents. Accordingly, under this logic, *Patani* provides equal "motivation" to substitute any of the hydrogens on the molecule of the *Hcaplus Abstract* with any of the possible bioisosterers. Given that there are eleven possible hydrogens in eight positions to be substituted on the *Hcaplus Abstract* molecule, and that each hydrogen could be substituted with Fl, OH, NH_2, CH_3, SH, CF_3, Cl, CN, OCH_3 and Br, dozens of possible combinations are born. The Examiner has demonstrated no motivation to select the CH_3 substituent out of those disclosed in *Patani* nor has she demonstrated any motivation to substitute that CH_3 for the hydrogen at the 2 position on the pyridyl ring of the *Hcaplus Abstract* molecule.

With respect to the *Blake* reference the Examiner has ignored the actual teachings of the reference and has decided to simply focus on the general premise, namely that "generally stable isotopes are proving useful as tracers for drug distribution and metabolism studies." (p. 6 of the Official Action). This general statement fails to provide one of ordinary skill in the art with the motivation to engage in the specific substitution required to arrive at the instantly claimed invention. When one reviews the actual teachings of *Blake* it makes clear that employing ^{14}C and ^{3}H as radiolabels are disadvantageous as compared with ^{13}C. (See Blake at p. 385). Thus, one of ordinary skill in the art would not be motivated by *Blake* to use any of the isotopes of the instantly claimed invention. Moreover, *Blake* provides no motivation to radiolabel the *Hcaplus*

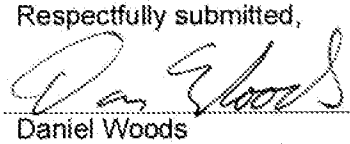
[2] *See* pages 7-8 of Applicant's response filed January 25, 2010.

Abstract compound nor is there any teaching in the *Hcaplus Abstract* or any other prior art that it would be advantageous to radiolabel said compound.

Additionally, the Examiner has provided no motivation to radiolabel the O-methyl oxime substituent of the *Hcaplus Abstract* compound. The invention of claim 1 (where R is methyl) of the instant application has 15 carbon atoms, 16 hydrogen atoms, two nitrogen atoms and one oxygen atom, any (or all) of which could be radiolabeled. There is no teaching in *Blake*, or any of the cited references, which would motivate one of ordinary skill in the art to radiolabel the O-methyl oxime substituent of the *Hcaplus Abstract* compound as opposed to any of the other atom in the structure. Moreover, there is no teaching in *Blake*, or any of the cited references, which would motivate one of ordinary skill in the art to radiolabel that position with ^{3}H or ^{11}C. Indeed, as mentioned previously, *Blake* teaches that there is a strong motivation to avoid ^{3}H, suggesting instead that ^{13}C should be employed. (p.385).

As the Examiner has failed to demonstrate why one of ordinary skill in the art would be motivated by the prior art teachings to modify the *Hcaplus Abstract* compound to both add a methyl group to the 2 position of the pyridyl ring and to radiolabel the O-methyl oxime substituent group with either ^{3}H or ^{11}C Applicant respectfully submits that a prima facie case of obviousness has not been established and request withdrawal of the pending rejection.

Respectfully submitted,



Daniel Woods
Attorney for Applicant
Reg. No. 59,864

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9587

Date: November 4, 2010